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BIOLOGICAL SYSTEMS IN TRANSITION: SENSITIVITY TO EXTREMELY LOW-FREQUENCY FIELDS

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ABSTRACT

It has been suggested for some time that cells "far from equilibrium" may be the most sensitive to applied extremely low-frequency (ELF) electric and magnetic fields. The problem with this statement is that it is nearly impossible to quantify these words as they apply to a biological system in such a way that the definition can become part of a mechanistic model. It is apparent, however, that the physiological state of the biological system being exposed to ELF fields is important. A review of the literature allows one to identify many studies that have involved the simultaneous exposure of "normal" and "healing" cells to ELF fields (such as normal bone and flesh at a non-union fracture site), with the result being that only the "healing" cells were measurably affected by the applied fields. The non-union fracture in bone may be one example of where the state of the biological system (bone) can be quantified. It is also apparent that the physiological state of the system must be important in the ELF-biological system

interaction since, for example, it would be surprising if an ELF field could increase biological activity that was already proceeding at the maximum rate. This paper examines the physiological state of the biological system and its importance in forming a mechanistic model of the interaction between ELF fields and the system.

INTRODUCTION

Intensive study in the past several years has firmly established that extremely low-frequency (ELF) electric and magnetic fields can cause a variety of changes in biological systems. The changes that have been reported include alteration of calcium binding in cerebral tissue (1), the release of calcium (Ca^{2+}) from chick cerebral tissue (2,3), alteration of motility in marine diatoms (4), changes in cellular transcription (5-7), the alteration of bone cell growth rates (8), and the inhibition of bone cell response to parathyroid hormone (9). These are only a few of the reported effects of ELF fields on biological cells and cell systems, but they show that the fields seem to cause a broad range of effects.

An accepted mechanism to explain even one of the above or, for that matter, any other reported effect has yet to emerge. A number of models have been proposed (10-17), and each has certain strengths and weaknesses, but no single model has been able to provide the necessary insight needed to obtain a definitive answer to the simple question of "why?" The pressure on researchers to identify a mechanisms of coupling of ELF fields to biological systems is becoming acute for several reasons. The concern about 60-Hz ELF fields being a public health hazard is steadily growing. With no predictive model with which to set safety limits on field values, it is probable that limits will be set that depend on emotion or oratory rather than fact. A second reason for the pressing need of a predictive model is that scientific credibility of experiments and data depends in part on reproducibility of experiments both in the same laboratory and among independent laboratories. Reproducibility has been lacking in this research field partly because it is not clear which variables and to what level of accuracy variables have to be controlled in order to ensure "identical" experiments. A final reason for the identification of the mechanism or model of interaction is simply that every effect must have a reasonable cause that can be explained within the framework of physical and biological "laws" with, perhaps, some modifications to explain new data. The elusiveness of the explanation for the coupling between ELF fields and biological systems is of growing concern since, as time passes, critics of the research field become bolder in suggesting that the lack of a mechanism of proof that no real effects exist.

This paper suggests that perhaps a point has been overlooked (or at least underemphasized) in many experiments and several of the proposed models. This point, the physiological state of the cell or cell system, is the focus of our discussion. The idea that the state of the cells is important in the search for an interaction model is not new. Adey has discussed nonequilibrium phenomena in connection with non-ionizing ELF fields and biological systems for a number of years (18), as has Findl (18a). Many researchers may suspect that the "state" of their particular biological system may play a role in how an ELF field couples to their system, but it is not clear

that most of them realize just how critical this point may be. The importance of the state of biosystem equilibrium could be stated as follows:

If a biosystem (cell *in vitro*, tissue, whole animal, etc.) is in a state such that there is a measurable net *change vs. time* (for instance growth vs. time, cell division vs. time, DNA replication vs. time), or if the net change is zero but the system is not in physiological steady state, it may well be responsive to ELF fields.

The above statment also suggests that since a living biosystem is dynamic along a change-vs.-time curve, it should not be surprising that sensitivity to ELF fields may change with time.

Figure 1 suggests how the summary statement might be applied for a non-union bone fracture. A set of bone cells might be in a state represented by the lower left part of the figure. The cells are in a quiescent state, perhaps slowly proliferating, but for some physiological reason effective bone repair does not occur even after a considerable length of time. It is well known that ELF fields applied at the site of the break can prompt healing of the bone in many cases (8). However, homeostatic cells near the break site, exposed to the same fields, do not seem to respond to the ELF fields. The latter cells would already be at the physiological steady-state level shown in Figure 1. It might be possible for the ELF fields to change the slope of the healing-vs.-time curve, but it seems certain that there is a maximum rate at which healing can occur. If the bone proceeds to heal at a predetermined rate after the application of the field, the ELF field would seem to be a kind of repetitive trigger, applied to a very slow process to move the positive net change of bone produced to a much higher level. If it is necessary to apply the ELF field continuously to achieve the physiological steady state, it is probable that the field is modifying the slope of the healing curve.

The considerations that might be drawn from Figure 1 are that the bone cells must change physiologically to go from the lower left part of the curve to the upper right part of the curve, that the most probable places on the curve for ELF fields to cause system change are at the lower knee and along the slope between the lower and higher biological states, and that change in the cells at the far right of the curve seems

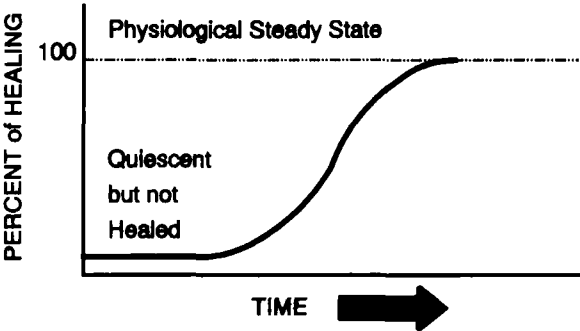


FIGURE 1. Hypothetical system change vs. time curve. The curve suggests that the biological system may be quiescent, but far from a final steady-state (healed) level, in the process of going between the two states, or at a physiological steady state where the net change (in bone produced for instance) is zero.

rather unlikely unless the ELF field could interrupt normal cell activity (which is not indicated by most data in the literature). A question might be formulated then:

What property of the cells at the lower left part of the curve does the ELF field modify to accelerate the healing process?

Identification of this property must necessarily involve the exposure of "non-union" bone cells to the ELF fields with the biological end-point of the experiment being selected by how the cells respond. It could take some time to discover exactly what is being changed by the ELF fields. By pinpointing the response, however, a path leading to the mechanism of interaction may be opened. It would also seem that an experiment that simply exposes normal bone cells to the ELF fields would be unable to address the question posed above.

DISCUSSION

There seems to be considerable experimental data to support the concept that non-equilibrium is a necessary condition for biological systems to be sensitive to ELF fields. In particular, if the literature on bone repair/ELF interactions is scanned, it is apparent that the applied fields seem to cause fracture healing, but cause no observable effects on the surrounding cells and tissue (20-24). That is rather remarkable. This point should also suggest the use of caution concerning ELF fields since embryonic systems may be especially sensitive to ELF fields (25-27) owing to prolonged and fairly rapid proliferation of cells in these systems. From the standpoint of elucidating a mechanism, it is difficult to quantify "nonequilibrium." That difficulty should not detour research along these lines, however. It is clear that certain cells and cell systems are more sensitive to the ELF fields. The challenge is to design experiments that will both identify and quantify the specific reason for this increased sensitivity.

Figure 2 illustrates an additional difficulty that must be considered in the design of the experiments discussed above. The dotted curve in Figure 2 can be viewed as a plot of the derivative of the curve in Figure 1. If the ELF field acts at the knee of the lower left part of the curve in Figure 1, and if the result is increased healing, the result could be the solid curve of Figure 2. The suggestion is that the ELF field caused a change at the knee, and then the healing process proceeded at a predetermined rate. If the experiment was set to run until time "A," the conclusion would be that the field was increasing at net bone being produced compared to the control. If the experiment was designed to run until time "B," it could be concluded that the field was having no effect at all. By the same reasoning, if the experiment was designed to run until time "C," the conclusion would be that the ELF field was causing the net bone being produced to be decreased compared to the control. A paper given at the 1991 Bioelectrical Repair and Growth Society (28) illustrated precisely these three possibilities in an experiment designed to study the effect of ELF on ossicles.

These curves could also shed light on the variability of seemingly identical experiments. If the response curves were very narrow, the times marked A, B, and C in Figure 2 would be much closer together. Thus, a small variation in the length of time allowed to elapse before the exposed and control systems were compared could produce any of the conclusions discussed above. Unless two laboratories make their mea-

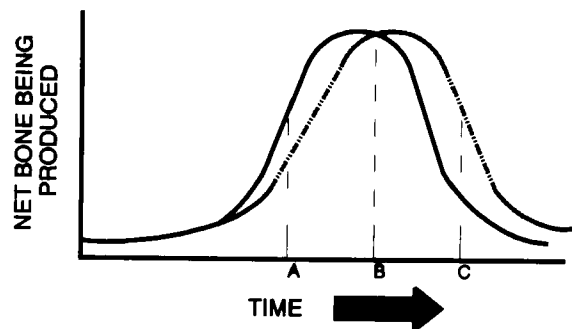


FIGURE 2. Hypothetical growth vs. time curves for an ELF-exposed (solid curve) and a control (dotted) biological system (such as a non-union bone break). The suggestion is that if the field acts to speed up the proliferation of bone cells in a healing system, these two curves could be the result. The times marked as A, B, and C draw attention to the fact that by comparing the exposed and control systems at these different times, one could reach entirely different conclusions about how the ELF fields were affecting the biological system.

surements at the same relative points in the biological process, they are likely to disagree as to the effect of the fields on the system, even though they are in fact performing the same experiment and obtaining the same results.

Both figures discussed above are idealized and hypothetical. They do represent biologically possible change or growth curves, however. It seems apparent that the activity state of biological systems must be given careful consideration in the formation of a realistic model that attempts to explain how ELF fields couple to such systems. Based on the observation that homeostatic cells or systems seem to be relatively insensitive to ELF fields, it could be argued that the equilibrium state of biosystems is, in fact, the key element in any model. Conversely, one could ask the question "what is necessary to move a set of cells or a biological system far enough from their normal state so that the cells or the system will become sensitive to the application of ELF fields?" A number of things come to mind, including initiation of embryonic growth, change of pH, change of the ambient temperature, and addition of chemicals such as growth-initiating or -inhibiting factors. It may be that no single factor can be identified as being able to sensitize all biological systems to ELF fields. However, identification and characterization of even one environmental sensitization factor may allow one to gain considerable insight into the mechanism of interaction, since the factor that causes the biosystem to respond to the ELF may help identify the site of interaction within the system.

EXPERIMENTAL EFFORTS

In the past several years, our group has investigated the interaction of a number of biological test systems with ELF fields. A specific interaction model—generally referred to as the cyclotron resonance or ion-specific resonance model (15,29-35)—was

being tested. All the results discussed below were obtained with the ELF magnetic fields set in accordance with the expression:

$$f_c = \frac{1}{2\pi} \frac{qB}{m} \quad (1)$$

where: f_c = the frequency of the applied ac magnetic field (Hz)

q = the specific ion charge (coulombs)

m = the specific ion mass (kg)

B = the value of the applied dc magnetic field (Tesla)

The biological systems that have been investigated include:

1. Marine diatoms (*Amphora coffeaeformis*)
2. Eight-day chick femurs, *in vitro*
3. Rabbits with fibular ostectomies
4. Mouse neuroblastoma (N-18) cells
5. Fava bean seeds/plants

Each system was chosen for a specific reason. The diatoms were known to have a motility vs. available extracellular calcium dose-response curve that looks very much like the curve shown in Figure 2 (33). The chick femur and the rabbit fibular ostectomy systems were studied to gain specific insight into how ion-resonant fields could influence bone growth in living systems. The transformed cell system was chosen for study as a means of determining how or if the resonant fields would alter cell proliferation in a "maximum growth" system. That is, it was assumed that the transformed cells would be proliferating at nearly the maximum possible rate. The fava bean seed experiments were undertaken when it began to appear that embryonic biological systems were sensitive to ELF fields. Fava bean seeds are large (legumes, about 1 cm long) and in the same family as peas and alfalfa. It was reasoned that the large seed would contain enough nutrients to allow significant plant growth over a 10-15 day experiment without having to add another variable (fertilizer). Also, the two other seeds mentioned above are of medium and very small size, respectively, thus allowing the possibility to extend the experiments to other seed sizes (and nutrient contents) while staying with the same plant family. Some of the major results from each of the five systems are discussed below, with particular emphasis on what seems to be the common thread between all the experiments. That thread, of course, is that each system was indeed far from steady state when an effect was engendered by the applied ELF magnetic fields.

Diatoms

Considerable data have been published on this biosystem (33-35). Originally, *A. coffeaeformis* was chosen for study because of its unique calcium ion vs. motility dose-response curve (see Ref. 33). The working hypothesis was that if increased movement of the Ca^{2+} ion across the cell membrane causes increased diatom movement, putting the diatoms on low-calcium agar plates (thus placing them near the lower left position in Fig. 1) and adding the calcium resonant fields should produce movement like that of diatoms on much higher-calcium plates. That is exactly what was observed. A point that has not been emphasized enough, however, is that the diatoms must be in the

log growth phase for this experiment to work. When stationary-phase is reached (beyond about 7 days in culture), the ELF-engendered effect also stops. Part of the protocol involves taking a few diatoms from the stock solution, allowing them to replicate for about 3 days in a large volume of the normal growth medium, completing two washes to remove excess calcium, and then using these diatoms for the experiment. Without this growth step, very little difference in motility is observed at any level of extracellular calcium, and hence no difference in movement is observed with the addition of the magnetic fields. Active replication of the diatoms is as critical to this experiment as is the removal of external calcium ions. In this case, it is also clear how the cells must be prepared to make them sensitive to the ELF fields.

Chick Femur

The next experimental system involved femurs taken from 8-day chick embryos (25), with the focal point of these experiments being the question of how ion-resonant magnetic fields would affect the growth of embryonic bone. Another variable studied with this biosystem was the amount of exposure time necessary to obtain an appreciable effect of the ELF field on the system. Since bone growth was involved, three ion-resonant frequencies were selected for the study. These were for the calcium, potassium, and magnesium ions. The data from the diatom studies indicated that the harmonics (multiples) of the fundamental frequency (3, 5, and 15) were important, and in the course of studying EQ. (1), it was observed that for calcium and magnesium, there was a harmonic overlap. For a dc magnetic field such as 20 μ Tesla (200 milligauss), the fifth harmonic frequency of calcium and the third harmonic frequency of magnesium are nearly equal. This overlap (shown as Ca/Mg on the figures) was also chosen for study since it appeared to be possible to obtain ion resonance for both ions simultaneously.

Figure 3 shows a typical response of the chick femur system. There was a general increase in the measured bone parameters when the biological system was exposed to resonant magnetic fields tuned for calcium, magnesium, and the 3/5 harmonic. Conversely, when the fields were tuned for the potassium ion, the exposed femurs showed a decrease in the measured parameters. Following the hypothesis of this paper, the chick femur system would appear to be in the central part of the curve of Figure 1. Figure 4 illustrates typical exposure time results with the femur system. It is interesting to see that length of time of exposure does indeed change the response of the femur system. For the diaphyseal collar thickness, it appears that a 1 h/day exposure is as effective as continuous exposure. As illustrated by Figures 2 and 4, time of exposure and the time it takes the biological system to move back to equilibrium are important to the dynamics of any experiment.

Rabbit Fibular Osteotomy

Two figures (Figs. 5 and 6) present data from the rabbit fibular osteotomy studies. The first of these studies involved 72 mature white rabbits (54 exposed, 18 controls) that underwent a fibular osteotomy of the left hindleg and a sham osteotomy on the right leg. The exposed rabbits were free-roaming in their cages and in the ion-resonant-tuned fields for 28 days. The controls lived in an identical cage/rack configuration in the same environmentally controlled room in the Montana State University Animal Resources Center (ARC). Figures 5 and 6 present just a small part of the data taken,

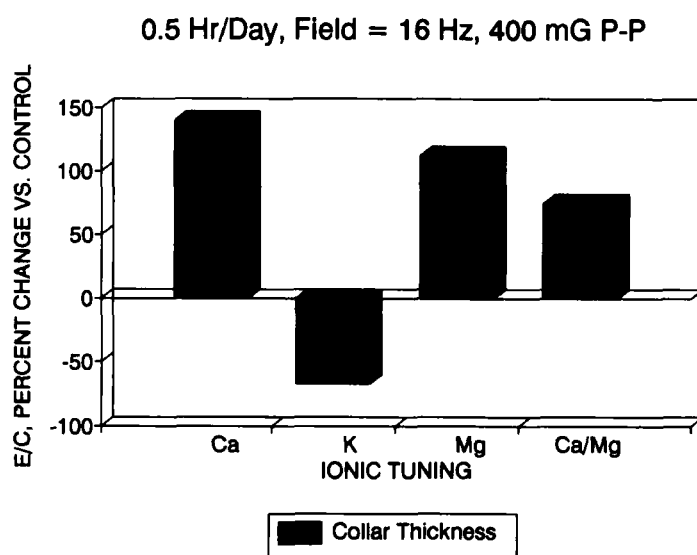


FIGURE 3. A sample of data from our specific ion resonance studies using the chick femur as the biological system. Shown in the percent change in the diaphyseal collar thickness using a 16-Hz, sinusoidal signal with the dc magnetic field set to obtain resonance for four different ions (that is, set for specific ion resonance). The $\text{Ca}^{2+}/\text{Mg}^{2+}$ bar shows the result obtained by exploiting the harmonic overlap for these two ions. At any dc magnetic field, the fifth harmonic frequency of the calcium ion is nearly equal to the third harmonic frequency of the magnesium ion. In this and all the following data, the ac and dc magnetic fields were parallel.

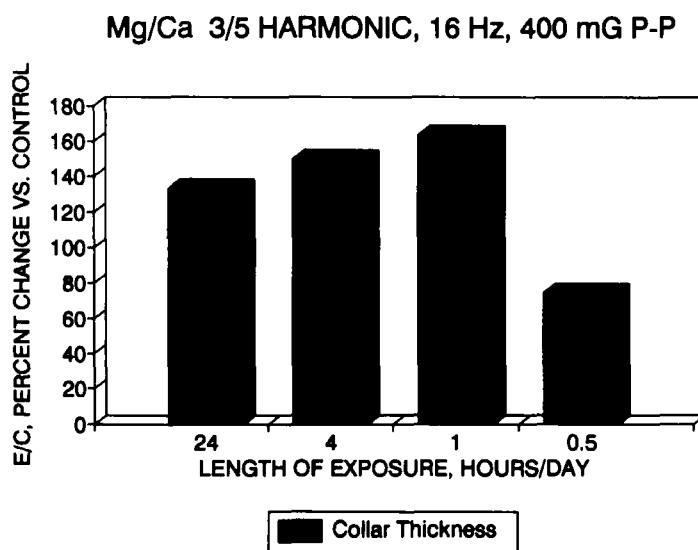


FIGURE 4. Further chick femur data showing the result of exposing the femurs to the 3/5 harmonic, sinusoidal signal for different duty cycles. It is interesting to note that the optimum duty cycle appears to be 1 h of exposure time per each 24 h.

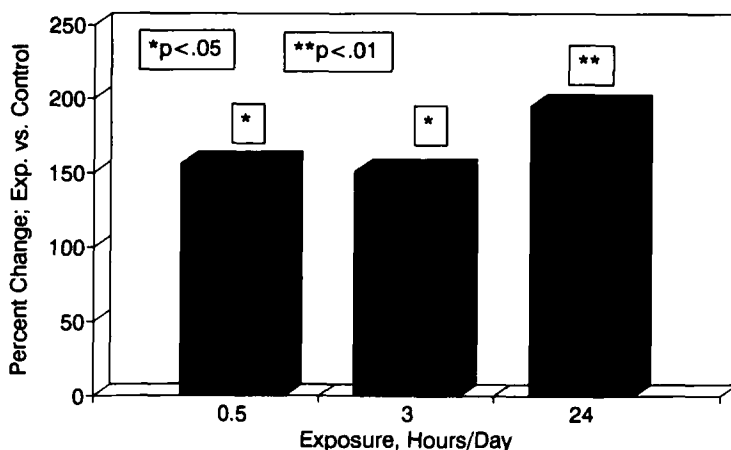


FIGURE 5. Typical data from our study of specific ion resonance and white rabbits that had undergone a fibular ostectomy. These data show the percent bone present (percent change vs. control) as we varied the exposure time. The dc magnetic field was set to maintain the resonant condition for the calcium ion with the sinusoidal ac magnetic field frequency maintained at 16 Hz. It is again seen that a duty cycle of 0.5 h/24 h produced a strong biological effect in the bones.

but they show that both calcium and magnesium ion resonances had a strong effect on the amount of bone present in the ostectomy site after the 28-day exposure period. For the magnesium ion in particular, it was observed that an exposure time of 0.5 h/24 h was sufficient to cause an increase in the percent bone present.

These rabbits also underwent a complete autopsy at the end of the experiments. No abnormalities could be detected in the body weights or histological appearance of any of the vital organs (brain, liver, heart, lungs, gonads, spleen) or muscle tissue.

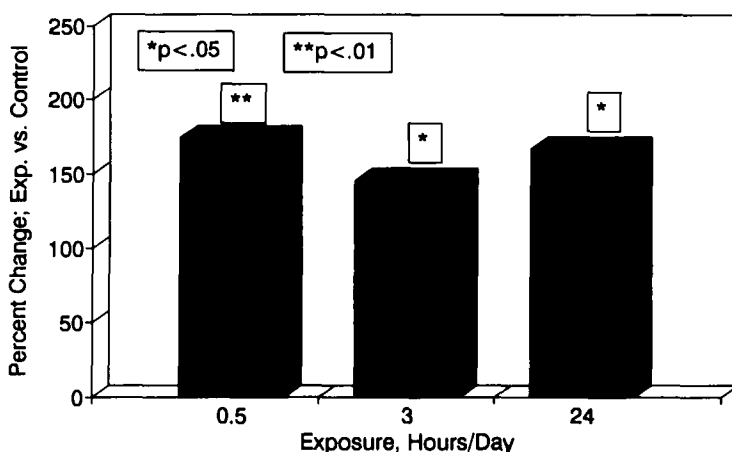


FIGURE 6. The same conditions were maintained as in Figure 5, but the target ion was magnesium.

A second, nearly identical experiment was then carried out, but this time the exposed rabbits lived in the resonant fields for 6 months after the osteotomy was performed. This experiment was done specifically to look for abnormal growth (either increased or decreased growth) or any indication of initiation of transformation of any cells. The autopsy on each rabbit at the end of the 6-month period was very complete (including complete blood analysis at the end and during the experiment) and was carried out by an independent veterinarian under strict guidelines. No abnormalities of any kind were found. *It appears that this biological system only responds to the ELF fields at the site of the osteotomy and then only when the cells responsible for bone repair have been moved into a "healing mode" by the operation.* After the limbs were healed (at about 36 days), no further induced alterations took place, as evidenced by the fact that at 6 months, only normal bones and animals were observed. There were no "super bones," no abnormally large or small rabbits, nor was there any evidence of cell transformation within the rabbits. The entire biological system became homeostatic and hence apparently not responsive to the ELF fields as soon as healing of the limb was completed.

N-18 Neuroblastoma

Transformed cells were originally chosen for study because we hypothesized that such cells would be near a maximum physiological state and undergoing a continuous rate of cell proliferation. It was, therefore, expected that the resonant magnetic fields would perhaps act to slow the rate of proliferation. Figure 7 suggests that this is not

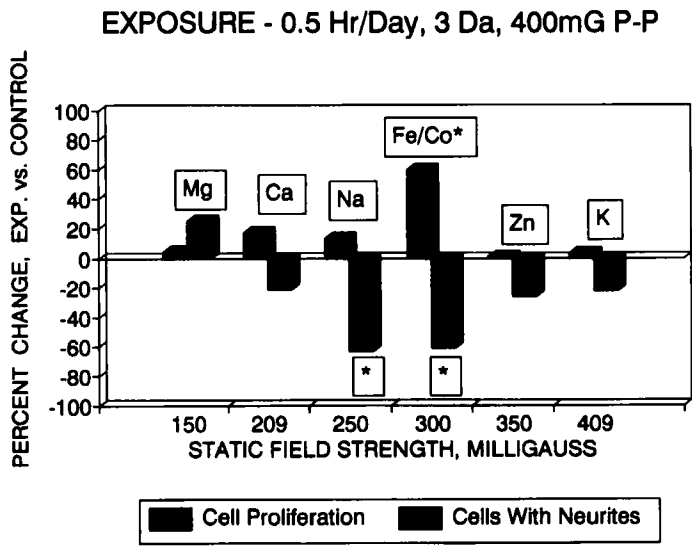


FIGURE 7. N-18 mouse neuroblastoma cells were exposed to the sinusoidal ac magnetic field with a fixed frequency of 16 Hz. The dc magnetic field was changed through this series of experiments from 15 μ Tesla to 40.9 μ Tesla in 5- μ Tesla steps. The data at (Ca) and (K) were taken with the dc field adjusted slightly (20.9 and 40.9 μ Tesla, respectively) to obtain the exact resonance conditions for these ions. Significant changes can be observed at 25 and 30 μ Tesla (250 and 300 milligauss). Both the observed changes could be viewed as making the cells "more threatening" to the host system.

the case for the N-18 mouse neuroblastoma cells. The cells were exposed in a series of experiments to an ac magnetic field with a fixed frequency of 16 Hz and with the parallel dc magnetic field varied in 5- μ Tesla steps from 15 to 40.9 μ Tesla. In the figure, the ion whose charge to mass ratio is nearest to resonance at the dc field value on the axis is shown on the bar. For calcium and potassium, the respective dc field values used were 20.9 μ Tesla and 40.9 μ Tesla in order to have 16 Hz be exactly the resonance frequency. The data indicate that the proliferation rate can be significantly increased over the controls, contrary to the original hypothesis. This suggests the N-18 cells were closer to the middle range in Figure 1 rather than the upper right range as expected. We have obtained similar results with other transformed cell lines (unpublished).

Figure 7 also shows another parameter measured for the N-18 cells, the number of cell processes. In this case, the ELF magnetic fields did cause a decrease in the number of processes formed by the exposed cells, compared to the controls. It is interesting to note in this case, however, that two ion resonances were identified as being able to significantly modify process formation. The data shown in Figure 7 illustrate two points that make experimental efforts to identify the ELF, biosystem mechanism of interaction very difficult without a theoretical model. First, it is difficult to predict, before an experiment is conducted, the biological parameter that should be examined for change once the biological system is exposed to the ELF fields (also note that the field caused an *increase* in one measured end-point, but a *decrease* in a second end-point). Secondly, one does not know exactly what field parameters to use for the exposure. The use of the ion resonance model has at least provided a framework from which to construct experiments in an orderly fashion. We feel a missing, but key, element of the model is the identification and quantification of the specific biological factor that sensitizes a biological system to the ELF fields.

Plant

The fava bean system was selected for study because it offered a convenient embryonic system that could be easily studied, with root mass, stem growth, and plant mass being the end-points. Each of these three parameters is easy to measure, and the entire experiment is so simple that it should not be difficult for other investigators to carry out identical experiments. This biological system has provided us with an intriguing set of data. The first experiments were carried out at the laboratory ambient temperature of about 24.5 °C. The magnetic fields were tuned for calcium ion resonance at 15.3 Hz. A very modest (15%), nonsignificant ($p = 0.157$) increase in root mass was seen. Shortly after these data were taken, the laboratory cooled to an ambient of about 18 °C, just after a new experiment was started. The results from this experiment indicated a significant increase (about 20%, $p < 0.001$) in the root and plant mass and stem height (exposed over control). These data suggested that temperature might be the factor that could vary the sensitivity of this biosystem to ELF magnetic fields.

It is well known that seeds of any species of plant will not sprout and grow below a certain characteristic temperature. This characteristic temperature may be different for different species of plant, but the zero point is approximately 4 °C. The data suggest that we may be displacing the system to somewhere nearer the lower part of a growth curve like that of Figure 1 by lowering the ambient temperature. With the addition of the ELF magnetic fields tuned for the calcium ion, the cooled biosystem

can perhaps be moved up along the growth curve to achieve more robust sprouting and growth. We are currently gathering further data on this biosystem's reaction to ELF fields vs. temperature. System response vs. frequency studies will then follow. The fava bean system may provide, for the first time, a direct controllable link between a biological system, its equilibrium state, and specific applied ELF magnetic fields.

CONCLUSIONS

We have presented an argument for including the physiological state of any biological system as an essential element for a model that can successfully predict how ELF fields will change growth processes in the biosystem. It is also suggested that as a result of this same reasoning, any biosystem in a state of dynamic change will have a response that will vary with time if it responds to the ELF fields. Thus, not only the state of the system, but also its rate of movement toward homeostasis and its position along that curve, are all factors to be considered when experiments are being designed to test a working hypothesis. It is possible that lack of attention to these points is a major factor in the nonreproducibility of many experiments in different laboratories.

It is recognized that quantifying the "physiological state" of any biological system is difficult. It would seem, therefore, that experiments should be designed using very well-known and very well-characterized biological systems. Candidate systems might include the dipteran *Sciara coprophila*, (6,7), the diatom *Amphora coffeaeformis*, (33,34), ossicle cells *in vitro* (28), and perhaps certain plant seeds such as the fava bean (this paper and Ref. 36). The references cited with each of the above biological systems each give data that ELF fields can couple to these systems to cause a measurable biological change. Although these systems are not "simple," they are well enough characterized that reasonable hypotheses can be formed and tested that may be able to pinpoint the site where the field is causing the biological change. By the same reasoning, it should be possible to study the importance of the physiological state of each system as this state pertains to the ELF sensitivity of the biological system.

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